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Press Release

Datopotamab Deruxtecan Demonstrated Meaningful Clinical Activity in Patients with Previously Treated Advanced EGFR-Mutated Non-Small Cell Lung Cancer in TROPION-Lung05 and TROPION-Lung01 Pooled Analysis

- Daiichi Sankyo and AstraZeneca's datopotamab deruxtecan showed a 42.7% objective response rate in previously treated patients
- Data support recent BLA submission in the U.S. for this patient population

Tokyo and Basking Ridge, NJ – (December 6, 2024) – A pooled analysis of the TROPION-Lung05 phase 2 and the TROPION-Lung01 phase 3 trials showed datopotamab deruxtecan (Dato-DXd) demonstrated clinically meaningful tumor response in patients with previously treated advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC). These data, along with progression-free and overall survival results from the analysis, were presented during a late-breaking proffered paper session (LBA7) at the 2024 ESMO Asia (#ESMOAsia24) Congress.

Datopotamab deruxtecan is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

Datopotamab deruxtecan demonstrated a confirmed objective response rate (ORR) of 42.7% (95% confidence interval [CI]: 33.6-52.2) in a pooled analysis of 117 patients with EGFR-mutated NSCLC from the TROPION-Lung05 (n=78) and TROPION-Lung01 (n=39) trials, as assessed by blinded independent central review (BICR). Five (4.3%) complete responses (CRs), 45 (38.5%) partial responses (PRs) and 48 (41.0%) cases of stable disease (SD) were observed. The median duration of response (DOR) was 7.0 months (95% CI: 4.2-9.8) and the disease control rate (DCR) was 86.3% (95% CI: 78.7-92.0). Median progression-free survival (PFS) was 5.8 months (95% CI: 5.4-8.2) and median overall survival (OS) was 15.6 months (95% CI: 13.1-19.0).

"Initial treatment with EGFR tyrosine kinase inhibitors has significantly improved outcomes for patients with advanced EGFR-mutated non-small cell lung cancer, but most patients eventually experience disease progression," said Myung-Ju Ahn, MD, PhD, Professor, Hematology-Oncology Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

“These results suggest datopotamab deruxtecan could offer patients with EGFR-mutated non-small cell lung cancer a much-needed option in the pre-treated metastatic setting.”

Results in patients previously treated with osimertinib were similar to the overall pooled population. In 96 patients previously treated with osimertinib, a confirmed ORR of 44.8% (95% CI: 34.6-55.3), as assessed by BICR was seen. Four (4.2%) CRs, 39 (40.6%) PRs and 37 (38.5%) cases of SD were observed. The median DOR was 6.9 months (95% CI: 4.2-9.8) and the DCR was 85.4% (95% CI: 76.7-91.8). Median PFS was 5.7 months (95% CI: 5.4-7.9) and median OS was 14.7 months (95% CI: 13.0-18.3).

The safety profile of datopotamab deruxtecan was consistent with previous reports from the TROPION-Lung05 and TROPION-Lung01 trials, with no new safety concerns identified. The most common treatment-related adverse events (TRAEs) of any grade were stomatitis (59%), alopecia (49%), nausea (46%), fatigue (18%), decreased appetite (16%), constipation (15%), vomiting (12%), rash (11%) and pruritus (10%). Grade 3 or higher TRAEs occurred in 23% of patients. Adverse events of special interest (AESI) of any grade were stomatitis, ocular surface events and adjudicated drug-related interstitial lung disease. No grade 4 or 5 stomatitis, ocular surface events or adjudicated drug-related ILD events occurred.

“Results of this pooled analysis show the potential for datopotamab deruxtecan in patients with EGFR-mutated non-small cell lung cancer with disease progression following multiple lines of prior treatment in the metastatic setting,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “The data from the TROPION-Lung05 and TROPION-Lung01 trials support our recent regulatory submission in the U.S. and highlight the potential of datopotamab deruxtecan to become a new treatment option for this patient population.”

“These results show that datopotamab deruxtecan can improve outcomes for patients with EGFR-mutated non-small cell lung cancer whose disease has become resistant to current treatments, and that it has potential to do so in patients harboring a range of EGFR mutations,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “These data, as well as our forthcoming trial in patients with TROP2-QCS biomarker-positive tumors, mark critical steps in our effort to follow the science and understand the full potential of datopotamab deruxtecan in later-line lung cancer settings.”

Patients in the pooled analysis received a median of three prior lines of treatment in the metastatic setting (range, 1-5). Eighty-two percent of patients were previously treated with osimertinib, including 40.2% in the first line and 29.1% in the second line.

In the pooled population, a range of EGFR mutations was observed, including exon 19 del, exon 21 L858R, exon 20 T790M, exon 18 G719X, exon 21 L861Q, exon 20 ins, and exon 20 C797S.

Summary of Pooled Results from TROPION-Lung05 and TROPION-Lung01

Efficacy Measure	EGFR-mutated Pool (n=117)	Prior Osimertinib (n=96)
Confirmed ORR, n (%) [95% CI][i,ii]	50 (42.7%) [33.6-52.2]	43 (44.8%) [34.6-55.3]
Median BOR, n (%)[i]		
CR, n (%)	5 (4.3%)	4 (4.2%)
PR, n (%)	45 (38.5%)	39 (40.6%)
SD, n (%)	48 (41.0%)	37 (38.5%)
Non-CR/Non-PD, n (%)	3 (2.6%)	2 (2.1%)
PD, n (%)	12 (10.3%)	10 (10.4%)
NE, n (%)	4 (3.4%)	4 (4.2%)
Median DOR, months (95% CI)[i]	7.0 months (4.2-9.8)	6.9 months (4.2-9.8)
DCR, n (%) (95% CI) [i, iii]	101 (86.3%) [78.7-92.0]	82 (85.4%) [76.7-91.8]
Median PFS, months (95% CI)[i]	5.8 months (5.4-8.2)	5.7 months (5.4-7.9)
Median OS, months (95% CI)	15.6 months (13.1-19.0)	14.7 months (13.0-18.3)

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

[i]As assessed by blinded independent central review

[ii]ORR is complete response + partial response

[iii]DCR is complete response + partial response + stable disease or non-complete response/non-progressive disease

About TROPION-Lung05

TROPION-Lung05 is a global, multicenter, single-arm, open-label phase 2 trial evaluating the efficacy and safety of datopotamab deruxtecan in patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed on at least one TKI (with or without other systemic therapies) and on or after one regimen of platinum-based chemotherapy. Patients receiving up to four prior lines of treatment with tumors with one or more genomic alterations including EGFR, ALK, ROS1, NTRK, BRAF, RET or MET were eligible for the trial.

The primary trial endpoint of TROPION-Lung05 is ORR as assessed by BICR. Secondary efficacy endpoints include DoR, DCR, clinical benefit rate (CBR), PFS, time to response (TTR), OS and safety.

TROPION-Lung05 enrolled 137 patients globally in Asia, Europe and North America. For more information visit ClinicalTrials.gov.

About TROPION-Lung01

TROPION-Lung01 is a global, randomized, multicenter, open-label phase 3 trial evaluating the efficacy and safety of datopotamab deruxtecan versus docetaxel in adult patients with locally advanced or metastatic NSCLC with and without actionable genomic alterations who require systemic therapy following prior treatment. Patients with actionable genomic alterations were previously treated with an approved targeted therapy and platinum-based chemotherapy. Patients without known actionable genomic alterations were previously treated, concurrently or sequentially, with platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor.

The dual primary endpoints of TROPION-Lung01 are PFS as assessed by BICR and OS. Key secondary endpoints include investigator-assessed PFS, ORR, DoR, TTR, and DCR as assessed by both BICR and investigator, and safety.

TROPION-Lung01 enrolled approximately 600 patients in Asia, Europe, North America, Oceania and South America. For more information visit ClinicalTrials.gov.

Primary PFS results and interim OS results from TROPION-Lung01 were presented at the 2023 ESMO (#ESMO23) Congress. Final OS results were presented at IASLC 2024 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC24) and simultaneously published in the *Journal of Clinical Oncology* in September 2024.

About Advanced Non-Small Cell Lung Cancer

Nearly 2.5 million lung cancer cases were diagnosed globally in 2022.[1] Lung cancer is broadly split into small or non-small cell lung cancer, the latter accounting for about 80% of cases.[2] Approximately 10% to 15% of patients with NSCLC in the U.S. and Europe, and 30% to 40% of patients in Asia have an EGFR mutation.[3,4] The majority of EGFR mutations occur in tumors of nonsquamous histology.[5]

For patients with tumors that have an EGFR mutation, the established first-line treatment in the metastatic setting is an EGFR TKI.[6] While EGFR TKIs have improved outcomes in the first-line setting, most patients eventually experience disease progression and receive subsequent therapies, such as chemotherapy.[7,8,9,10]

TROP2 is a protein broadly expressed in the majority of NSCLC tumors.[11] There is currently no TROP2 directed ADC approved for the treatment of lung cancer.[6,12]

About Datopotamab Deruxtecan (Dato-DXd)

Datopotamab deruxtecan (Dato-DXd) is an investigational TROP2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, datopotamab deruxtecan is one of six DXd ADCs in the oncology pipeline of Daiichi Sankyo, and one of the most advanced programs in AstraZeneca's ADC scientific platform. Datopotamab deruxtecan is comprised of a humanized anti-TROP2 IgG1 monoclonal antibody, developed in collaboration with Sapporo Medical University, attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

A comprehensive global clinical development program is underway with more than 20 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple cancers, including NSCLC, triple negative breast cancer and HR positive, HER2 low or negative breast cancer. The program includes seven phase 3 trials in lung cancer and five phase 3 trials in breast cancer evaluating datopotamab deruxtecan as a monotherapy and in combination with other anticancer treatments in various settings.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019 and datopotamab deruxtecan (Dato-DXd) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and datopotamab deruxtecan.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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